The Stem Cell Research Environment

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The Stem Cell Research Environment: A Patchwork of Patchworks

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Abstract Few areas of recent research have received as much focus or generated as much excitement and debate as stem cell research. Hope for the therapeutic promise of this field has been matched by social concern associated largely with the sources of stem cells and their uses. This interplay between promise and controversy has contributed to the enormous variation that exists among the environments in which stem cell research is conducted throughout the world. This variation is layered upon intra-jurisdictional policies that are also often complex and in flux, resulting in what we term a 'patchwork of patchworks'. This patchwork of patchworks and its implications will become increasingly

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important as we enter this new era of stem cell research. The current progression towards translational and clinical research among international collaborators serves as a catalyst for identifying potential policy conflict and makes it imperative to address jurisdictional variability in stem cell research environments. The existing patchworks seen in contemporary stem cell research environments provide a valuable opportunity to consider how variations in regulations and policies across and within jurisdictions influence research efficiencies and directions. In one sense, the stem cell research context can be viewed as a living experiment occurring across the globe. The lessons to be gleaned from examining this field have great potential for broad-ranging general science policy application.

Keywords Stem cell research · Policy · Regulation · International · Collaboration · Harmonization

Introduction

Few areas of recent research have received as much focus or generated as much excitement and debate as stem cell research. It has captured the attention of policymakers, the popular press, funding agencies, patient groups and the general public. Hopes regarding the therapeutic promise of this field are countered by social concerns associated largely with the sources of stem cells and their uses. This interplay between promise and controversy has contributed to the enormous variation that exists among the environments in which stem cell research is conducted in different jurisdictions around the world. Such variation is layered upon intra-jurisdictional policies that are also often complex and in flux. The resulting multifaceted and, at times, overlapping and discordant regimes present both within and between different jurisdictions constitute what we term a 'patchwork of patchworks'.

This patchwork of patchworks and its implications are increasingly important in light of a number of strong indications that we are entering a new era in the field of stem cell research. New sources of stem cells and stem cell research technologies are emerging including, among others, induced pluripotent stem cells and interspecies somatic cell nuclear transfer. These research tools hold great promise for enlarging the frontiers of biological understandings and advancing drug development, while also raising fresh ethical and legal concerns [1–3]. Further, new clinical advances are coming to the fore, novel funding sources are emerging, and political landscapes in some jurisdictions, most notably the United States (U.S.) [4], are being transformed, raising the possibility that major changes in research and funding policies will result. Importantly, the U.S. Food and Drug Administration (FDA) recently issued its first approval for clinical trials using the products of human embryonic stem cells [5]. In addition, these developments are occurring in the midst of a world-wide economic crisis in which efficiency is particularly important and competition for resources is increasing.

This current progression towards translational and clinical research among international collaborators serves as a catalyst for identifying potential policy conflict and makes it imperative to address jurisdictional variability in stem cell research environments. Doing so necessitates analyzing the variables relevant to this area of research and considering the influence of this variability on research and its downstream application, so as to gather knowledge and understandings that will provide the tools necessary to navigate these complexities effectively. It will be important to pursue these ends in a manner that respects different cultural, social and religious norms and values, while encouraging the realization of the potential social benefits of stem cell research.

Stem cell research is not unique in its complexity. There are many areas of research with jurisdictional variations (e.g. genomics and genetically modified organisms). However, the existing patchworks seen in contemporary stem cell research environments appear particularly acute. Given the tremendous

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commitment to this area of research shown by the scientific community, policy makers and funders, and the level of excitement it engenders in the public, it provides a valuable opportunity to consider how variations in regulations and policies across and within jurisdictions influence research efficiencies and directions. In one sense, the stem cell research context can be viewed as a living experiment occurring across the globe and the lessons to be gleaned from examining this developing field have great potential for broad-ranging general science policy application.

In order to initiate this complex analysis, we gathered an international group of scholars from a variety of disciplines with the dual purposes of forming a picture of the current lay of the land of the international stem cell research environment, and of identifying key areas requiring further investigation.[1] The research presented in the papers accompanying this introductory piece provided the groundwork for this initiative.[2] These supporting papers address a number of key areas of study including public perceptions regarding stem cell sources and policies, international policy interoperability and harmonization in stem cell research, perspectives of scientists and researchers regardi ng the ethical issues of stem cell research, and the themes currently emerging in discourse surrounding stem cell research. This research served to inform the initial exploration presented here, and will provide the foundation for ensuing examination and analysis.

A Complex Patchwork

It has been widely noted that there are clear and profound differences in how jurisdictions regulate stem cell research [6, 7] (see Side Bar). Some countries permit human embryonic stem cell research (hESC) with imported lines only and prohibit the derivation of new hESC lines from excess IVF embryos and somatic cell nuclear transfer (SCNT) (e.g. Germany & Italy). Some jurisdictions permit both (e.g., the United Kingdom ("U.K.")), while others prohibit both (e.g., Ireland). Other countries permit hESC research and the derivation of new hESC lines from supernumerary IVF embryos, but prohibit SCNT (e.g., Denmark & Canada). Some nations (e.g., Argentina) have no laws explicitly governing hESC research, while others have significant variation within their borders. Consider, for example, the patchwork of regulations that has emerged within the U.S., where states differ dramatically on various regulatory issues regarding hESC research including the procurement of gametes, embryos, and other cells from human donors, the derivation of new hESC lines, and the use(s) of these lines [8]. In addition to these types of policies, there are many other forms of variation that add to the complexity of the patchwork.

Public perception of stem cell research varies widely around the world. Given the plurality of religious and cultural norms that often inform positions on stem cell research globally [9], this variance is to be expected. Research shows that the derivation of stem cells from certain sources has served as a flashpoint for controversy and debate, particularly around the use of human embryos. A recent comparison of nine European countries found a plurality of perceptions on embryo research, ranging from the view that human embryos have the same status as live human beings (e.g., Austria and Germany), to the view that human embryos in their earliest stages are not yet sufficiently developed to constitute individual human entities (e.g., Denmark and the U.K.) [10]. SCNT, while receiving less research attention, has been shown to elicit greater resistance among U.S. [11] and U.K. publics [12] than has hESC research.

Public views are moderated by worldviews including attitudes and trust toward science, scientists and regulatory institutions, religiosity, media use, and gender, among other factors [13–15]. While public opinion patterns seem broadly suggestive of policy directions [16], and at times are implicated in policy making discourse [17], there is little evidence to date that policy preferences are directly linked to public views and the role public opinion plays in the policy making process varies considerably. In some cases, policy makers explicitly use public opinion to inform their decision making processes - for example, the U.K.'s Human Fertilisation and Embryology Authority's public consultation on hybrids and chimeras [18] - but in others, there is apparent discrepancy between public opinion and policy. Further research is required to illuminate the relationship between public opinion, policy and science reality across jurisdictions.

Patent policy provides an excellent example of variance as the role and appropriateness of strong patent legislation in the biotechnology field remains subject to debate [19–21]. Nonetheless, industry—especially biotech and pharmaceutical corporations—research funding agencies, governments and other entities often view patents as an essential element of the commercialization process and as a key factor in promoting innovation and economic stimulus [22, 23]. In the area of stem cell research, there is significant international variation in what is deemed patentable. In the U.S., embryonic stem cell lines are clearly patentable (e.g., Thomson, J.A. U.S. Patent No.

[1] The international workshop, "Lay of the Land", took place in Montreal, PC on January 15–16, 2009, as part of a Stem Cell Network funded project, "The Stem Cell Research Environment: Drawing the Evidence and Experience Together".

[2] A condensed version of this article, entitled "International stem cell environments: a world of difference", was published in Nature Reviews Stem Cells, online: 16 April 2009 | doi:10.1038/stemcells.2009.61.

5,843,780 (1998); Thomson, J.A. U.S. Patent No. 6,200,806 (2001)) [24]. Conversely, the European Patent Office recently came to the opposite conclusion and refused to grant a patent covering the use of hESC, using the public order and morality grounds [25]. In other jurisdictions (e.g., Canada) the future of embryonic stem cell research patents is less clear. The impact these differing patent policies will have on research remains uncertain and will require ongoing monitoring.

The funding of stem cell research and the focus on commercialization also varies by jurisdiction. In some jurisdictions, such as Singapore and California, stem cell research is part of a special state-sponsored economic and scientific platform and its funding is part of a specific strategic initiative [26]. In others, research in the area is primarily supported through science funding mechanisms typical of the jurisdiction such as government funding, granting agencies and foundations (e.g., U.K. and Canada). In some jurisdictions, namely parts of the U.S., there is limited funding available through the traditional sources (i.e. federal granting agencies), and it comes with limitations. Arguably, various dynamics are implicated in these differing approaches including economic, political and social variables.

Many other factors add to the complexity of this story of variation in research environments. There are jurisdictional differences in clinical trial regulations including the use of biologics, privacy rules, informed consent and assessment of risk. Research ethics norms associated with donation of embryos and tissues vary between jurisdictions and at times are undefined, influx or developing within given jurisdictions [27, 28]. Relevant research practice standards, including both research conduct and technical standards relating to cell line derivation and maintenance, are not universal. Another factor that cannot be overlooked relates to jurisdictional research capacity which is increasingly important as the field becomes more technologically complex. Clinical trial capacity and industry receptor capacity also significantly impact the nature and extent of the research being conducted. Finally, the capacity of different health care systems to respond to clinical developments and to address issues of access and social justice must be considered. Variation in all of these areas is reflective of both policy and funding factors.

It must be noted that there are a number of emerging recommendations and policy activities occurring at both national and international levels (e.g., the International Society for Stem Cell Research (ISSCR); the Interstate Alliance (U.S.), and the UNESCO Statement) that are part of an effort to promote greater harmonization in regulations, coordinate the ethical review of stem cell lines and materials, and promote transparency and enforcement of existing regulations. Nevertheless, different understandings regarding core values and principles endure between (and amongst) policy makers, civil society representatives and researchers. At times, these differences lead to disagreements, fragmentation or uncertainty about what constitutes appropriate conduct in different jurisdictions and settings.

Influence and Relevance of the Patchwork

While the data are still emerging, it seems axiomatic that the variability outlined above will impact the research environment. However, the nature of this impact remains undetermined and is why systematic analyses of the different variations, both individually and in combination, are critical. Even within jurisdictions, many of the variables are often in flux which can make it particularly challenging to trace impact and make connections. Given the number of elements that might be at work in any given context, an added conundrum is identifying and measuring the specific influential factors and their respective impact(s).

Divergent research environments, particularly policy frameworks and governing regulations, inevitably affect the conduct of stem cell research, including procurement, derivation, banking, distribution and use of stem cell lines. Variability arguably has the potential to introduce inefficiencies related to the sharing of materials and data and to the production of research. It may inhibit collaboration at both national and international levels, and restrict the flow of research and researchers [29]. It is also likely to have an impact on clinical translation. For example, concerns about past histories of various stem cell lines because of differing consent standards—in the absence of grandfathering clauses—could cause reticence by some institutions and/or researchers to use some lines [30]. Moreover, policy variations regarding the use of monetary payments for the donation of human reproductive materials and other ethical standards may also hinder research. For instance, several jurisdictions prohibit the importation of gametes and stem cell lines that have not been procured in accordance with local regulations [31]. Accordingly, a line derived through an egg sharing procurement arrangement in the U.K. may not be eligible for study using California Institute of Regenerative Medicine funding. A key challenge in addressing such policy variability is to identify what degree of consistency is required for effective cooperation, and what mechanisms can be used to manage differences. Actors in one jurisdiction may recognize a policy adopted in another as being substantially equivalent provided that it complies with certain basic principles, even if some differences remain. On other matters, they might demand strict policy convergence. Identifying clear and transparent rules will facilitate more efficient research conduct.

The nature of the international stem cell research environment patchwork also provides an opportunity to

explore the impact of different research environments and policies on scientific productivity. For example, do permissive regulatory approaches translate to increased productivity, or is this connection overstated? There is tentative evidence that policy variation may impact research outputs [32, 33]. However, more nuanced research is required to illuminate the prevalent factors. Another key issue is what impact intellectual property protections have on innovation and collaboration [34]. At the present time, it is challenging for researchers to assess whether patents encourage or discourage innovation globally [35, 36]. However, focusing specifically on the stem cell patent patchwork, it is possible to develop accurate patent landscapes [37] and to identify the more visible hurdles [38, 39] raised by patenting laws and practices, in order to inform future policy decisions. These different regimes present scholars of innovation with a sort of laboratory for studying the impact of the regulatory environment on research and development.

In addition to its impact on productivity and efficiency, the patchwork is also associated with potential human and ethical costs. Stem cell tourism, where often desperate patients seek treatment or participation in 'medical innovations' outside of clinical trials in jurisdictions with lax regulations for human subjects research, thereby exposing themselves to significant physical and financial risk, serves as a particularly concerning illustration of these costs. This issue has recently received international attention [40, 41]. When combined with 'forum shopping' by researchers who move to jurisdictions where they can work in a less regulated manner [42], these real but avoidable harms to patients may also impede the progress of stem cell science. International efforts are necessary to address this issue, particularly given that some jurisdictions simply do not have the capacity to implement FDA-style regulation. The movement of scientists and research workers (including trainees) across international borders also raises the issue of ethics education—or what might be labeled ethics re-orientation of migrant scientists. While these efforts require resources, they may also stimulate the cross-cultural comparison of norms. The intersection between the international science ethos and local ethical cultures makes studying different ways of providing ethical education to researchers a matter of some significance.

Notwithstanding the foregoing issues, as stem cell research is a controversial area that engages various ethical, religious, intellectual, social and cultural beliefs, some degree of variation in policy and perspective is clearly healthy and inevitable. Further, plurality invites innovative approaches and unique perspectives, and permits balance between extremes. The current patchwork is potentially responsible for the pursuit of different technologies, diverse training and varied discoveries. It also reflects the broad diversity of opinion and belief evident between people around the world and, at times, encourages novel collaborations (both scientific and political) and unlikely partnerships. As such, the existence of a patchwork is not necessarily detrimental. In addition, given the many underlying norms at play in this area there are some issues, including those such as the moral status of the embryo, patenting human biological material, and ethical issues surrounding gamete donation, on which agreement is unlikely.

However, in other areas such as research standards, clinical readiness, cell line quality and scientific integrity, policy uniformity appears more attainable and beneficial. The International Stem Cell Banking Initiative, the ISSCR's Registry of Provenance of Human Embryonic Stem Cell Lines and the European Commission's European Human Embryonic Stem Cell Registry serve as examples of efforts to promote international cooperation for research and clinical purposes [43]. The varying opportunities to find common ground on particular issues can be viewed on a continuum of flexibility, as represented in Fig. 1. Adopting this approach permits focused consideration of the areas most likely to benefit from efforts towards improved interoperability.

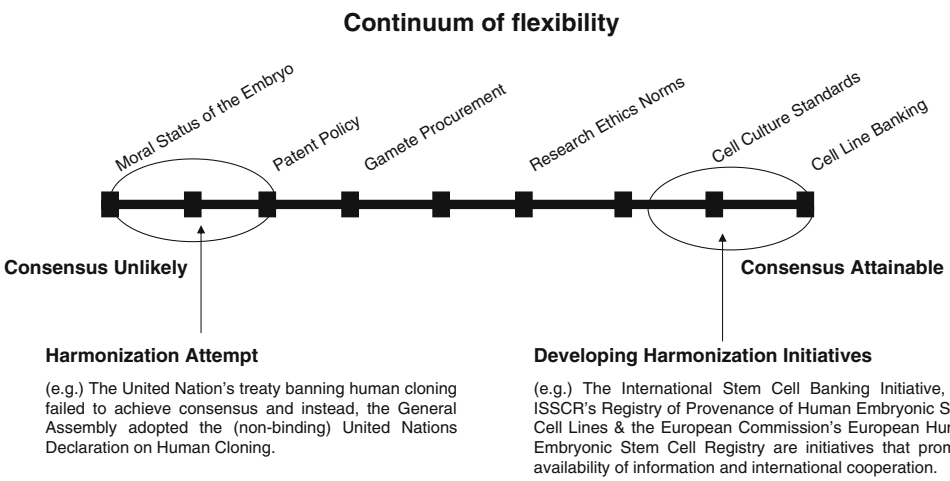

Fig. 1 Continuum of flexibility

Conclusion

While data regarding the impact of variation in research contexts is still emerging, at a minimum it seems safe to say that the story is more complex than is often expressed and cannot be reduced to the permissiveness or restrictiveness of any given jurisdiction(s) [44]. Factors including, but not limited to, jurisdictional capacities, funding and commercialization policies, patent policy, research ethics, technical standards, public opinion, and social norms all have an impact on the stem cell research environment. The resulting implications will affect the development of clinical knowledge, scientific talent, fundamental knowledge, and research tools, but further analysis is necessary to determine the nature and quality of that impact. When there has been such extensive investment in an area of research, as there has been with stem cell research—financially, politically and in the hopes of patients—and yet little clinical realization of this potential promise to date, it seems essential that we examine the factors driving the development of this area so that we are better positioned to enhance its future progress.

Recognizing and then examining the current patchwork of patchworks evident in the stem cell research environment also provides an opportunity to assess the impact of science policy and social context generally, with a view to informing the future direction of policy development and to improving efficiency and interoperability, where appropriate. One of the potential benefits of improving on the inefficiencies resulting from policy variance may be to assist stakeholders to benefit from new knowledge and scientific innovation in a more timely manner, which is a natural aim of therapeutically focused scientific research. We are not the first group to note these complexities [45], nor do we purport to have all the answers. This article, and the research published alongside it, will encourage further thought, analysis and investigation into the various issues raised by the patchwork of patchworks and will serve as a basis for a more broadly based and fruitful discourse, and for further investigative study.

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Side Bar A Case Study: Australia, Canada & the United Kingdom – three similar countries with stark policy variations

The complexity of the story underlying stem cell research policy is particularly acute in the stark policy variations evident in the legislative approaches adopted by Australia, Canada and the U.K. to SCNT and interspecies somatic cell nuclear transfer (iSCNT). The main difference between both technologies is the source of ova which acts as a receptacle for the nucleus of the somatic cell – human ova in SCNT, and animal ova in iSCNT. In Australia, iSCNT is prohibited but SCNT is permitted; in Canada the converse is likely true, while in the U.K. both are allowed. These three nations are culturally similar jurisdictions with comparable political systems and religious backgrounds, and yet they have arrived at very different policy standpoints on these contentious issues. The question is why?

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